

Marked up version of claims showing all revisions:

1. (Amended) A method for modifying the function of a target receptor associated with a neurological disorder in a subject comprising:

[administering a vaccine comprising] inducing the presence of a therapeutically effective amount of an antigen in the circulatory system of the subject, wherein the antigen elicits the production of antibodies that, upon compromise of the blood-brain barrier, will pass into the central nervous system of the subject and [in the circulatory system of the subject, or a composition comprising a therapeutically effective amount of an isolated antibody, or an antibody portion, wherein the antibodies] bind to a target receptor located on a neuronal cell in the central nervous system of the subject and associated with a neurological disorder, and modify the function of the target receptor[, such that modifying the function of the target receptor protects against a neurological disorder].

6. (Amended) The method of claim 1, wherein the [vaccine comprises an] antigen present in the circulatory system of the subject is selected from the group consisting of neurotransmitters, neuroreceptors, transporters, ion channels, signal transduction molecules, enzymes involved in the synthesis or degradation of neurotransmitters, growth factors, transcription factors, and cell surface molecules.

9. (Amended) [The method of claim 1] A method for modifying the function of a target receptor associated with a neurological disorder in a subject comprising:

inducing the presence of a therapeutically effective amount of an antigen in the circulatory system of the subject, wherein the antigen elicits the production of antibodies that, upon compromise of the blood-brain barrier, will pass into the central nervous system of the subject and bind to a target receptor located on a neuronal cell in the central nervous system of the subject and associated with a neurological disorder, and modify the function of the target receptor, wherein the presence of a therapeutically effective amount of the antigen in the circulatory system of the subject is induced by a vaccine [is] selected from the group consisting of a viral vector vaccine, a DNA vaccine, a peptide vaccine and a crude antigen vaccine.

22. (Amended) A method for modifying the function of a target receptor associated with a neurological disorder in the central nervous system of a subject comprising:

[administering a vaccine comprising] inducing the presence of a therapeutically effective amount of an antigen in the circulatory system of the subject, wherein the antigen elicits the production of antibodies that, upon compromise of the blood-brain barrier, will pass into the central nervous system of the subject and [in the circulatory system of the subject, or a composition comprising a therapeutically effective amount of an isolated antibody, or an antibody portion, wherein the antibodies] bind to the target receptor located on a neuronal cell in the central nervous system and associated with a neurological disorder, and directly [modifies] modify the function of the target receptor, or indirectly [modifies] modify the function of a process involving the target receptor[, such that the direct, or indirect modification protects against a neurological disorder].

24. (Amended) The method of claim 22, wherein the target protein is selected from the group consisting of neurotransmitters, neuroreceptors, transporters, ion channels, signal transduction molecules, enzymes involved in the synthesis or degradation of neurotransmitters, growth factors, transcription factors and cell-surface molecules.

25. (Amended) The method of claim 22, wherein the [vaccine comprises an] antigen present in the circulatory system of the subject is selected from the group consisting of neurotransmitters, neuroreceptors, transporters, ion channels, signal transduction molecules, enzymes involved in the synthesis or degradation of neurotransmitters, growth factors, transcription factors and cell surface molecules.

29. (Amended) [The method of claim 22] A method for modifying the function of a target receptor associated with a neurological disorder in the central nervous system of a subject comprising:

inducing the presence of a therapeutically effective amount of an antigen in the circulatory system of the subject, wherein the antigen elicits the production of antibodies that, upon compromise of the blood-brain barrier, will pass into the central nervous system of the subject and bind to the target receptor located on a neuronal cell in the central nervous system

and associated with a neurological disorder, and directly modify the function of the target receptor, or indirectly modify the function of a process involving the target receptor, wherein the presence of a therapeutically effective amount of the antigen in the circulatory system of the subject is induced by a vaccine [is] selected from the group consisting of a viral vector vaccine, a DNA vaccine, a peptide vaccine and a crude antigen vaccine.

36. (Amended) A method for modifying the function of a target receptor associated with cognition in the central nervous system of a subject comprising:

[administering a vaccine comprising] inducing the presence of a therapeutically effective amount of an antigen in the circulatory system of the subject, wherein the antigen elicits the production of antibodies that, upon compromise of the blood-brain barrier, will pass into the central nervous system of the subject and [in the circulatory system of the subject, or a composition comprising a therapeutically effective amount of an isolated antibody, or an antibody portion, wherein the antibodies] bind to the target receptor associated with cognition, and [modifies] modify the function of the target receptor such that the modification of the target receptor improves cognition in the subject.

38. (Amended) The method of claim 36, wherein the [vaccine comprises an] antigen present in the circulatory system of the subject is selected from the group consisting of neurotransmitters, neuroreceptors, transporters, ion channels, signal transduction molecules, enzymes involved in the synthesis or degradation of neurotransmitters, growth factors, transcription factors and cell surface molecules.

41. (Amended) [The method of claim 36,] A method for modifying the function of a target receptor associated with cognition in the central nervous system of a subject comprising:

inducing the presence of a therapeutically effective amount of an antigen in the circulatory system of the subject, wherein the antigen is induced by a vaccine [is] selected from the group consisting of a viral vector vaccine, a DNA vaccine, a peptide vaccine and a crude antigen vaccine, such that the antigen elicits the production of antibodies that, upon compromise of the blood-brain barrier, will pass into the central nervous system of the subject and bind to the

target receptor associated with cognition, and modify the function of the target receptor such that the modification of the target receptor improves cognition in the subject.

54. (Amended) A method for modifying the function of a target receptor associated with a neuroendocrine disorder in the central nervous system of a subject comprising:

[administering a vaccine comprising] inducing the presence of a therapeutically effective amount of an antigen in the circulatory system of the subject, wherein the antigen elicits the production of antibodies that, upon compromise of the blood-brain barrier, will pass into the central nervous system of the subject, and [in the circulatory system of the subject, or a composition comprising a therapeutically effective amount of an isolated antibody, or an antibody portion, wherein the antibodies] bind to the target receptor located on a neuronal cell in the central nervous system of the subject and associated with a neuroendocrine disorder, and directly [modifies] modify the function of the target receptor, or indirectly [modifies] modify the function of a process involving the target receptor[, such that the direct, or indirect modification protects against a neuroendocrine disorder].

59. (Amended) [The method of claim 54,] A method for modifying the function of a target receptor associated with a neuroendocrine disorder in the central nervous system of a subject comprising:

inducing the presence of a therapeutically effective amount of an antigen in the circulatory system of the subject, wherein the antigen is induced by a vaccine [is] selected from the group consisting of a viral vector vaccine, a DNA vaccine, a peptide vaccine and a crude antigen vaccine[.], such that the antigen elicits the production of antibodies that, upon compromise of the blood-brain barrier, will pass into the central nervous system of the subject, and bind to the target receptor located on a neuronal cell in the central nervous system of the subject and associated with a neuroendocrine disorder, and directly modify the function of the target receptor, or indirectly modify the function of a process involving the target receptor.

68. (Amended) The method of claim 54, wherein the target protein is selected from the group consisting of neurotransmitters, neuroreceptors, transporters, ion channels, signal transduction molecules, enzymes involved in the synthesis or degradation of neurotransmitters, growth factors, transcription factors and cell surface molecules.

86. (Amended) A method for modifying the function of an N-methyl-D-aspartate (NMDA) target receptor associated with a neurological disorder in a subject comprising:

[administering a vaccine comprising] inducing the presence of a therapeutically effective amount of an NMDA antigen in the circulatory system of the subject, wherein the antigen elicits the production of NMDA antibodies that, upon compromise of the blood-brain barrier, will pass into the central nervous system of the subject and [in the circulatory system of the subject, or a composition comprising a therapeutically effective amount of an isolated NMDA antibody, or an antibody portion, wherein the antibodies] bind to an NMDA target receptor located on a neuronal cell in the central nervous system of the subject and associated with a neurological disorder, and modify the function of the NMDA target receptor[, such that modifying the function of the NMDA target receptor protects against a neurological disorder].

91. (Amended) [The method of claim 86,] A method for modifying the function of an N-methyl-D-aspartate (NMDA) target receptor associated with a neurological disorder in a subject comprising:

inducing the presence of a therapeutically effective amount of an NMDA antigen in the circulatory system of the subject, wherein the antigen is induced by a vaccine [is] selected from the group consisting of a viral vector vaccine, a DNA vaccine, a peptide vaccine and a crude antigen vaccine[.], such that the antigen elicits the production of NMDA antibodies that, upon compromise of the blood-brain barrier, will pass into the central nervous system of the subject and bind to an NMDA target receptor located on a neuronal cell in the central nervous system of the subject and associated with a neurological disorder, and modify the function of the NMDA target receptor.

95. (Amended) A method for modifying the function of a N-methyl-D-aspartate (NMDA) target receptor associated with a neurological disorder in the central nervous system of a subject comprising:

[administering a vaccine comprising] inducing the presence of a therapeutically effective amount of an NMDA antigen in the circulatory system of the subject, wherein the antigen elicits the production of NMDA antibodies in the circulatory system of the subject that, upon compromise of the blood-brain barrier, will pass into the central nervous system of the subject and [, or a composition comprising a therapeutically effective amount of an isolated NMDA antibody, or an antibody portion, wherein the NMDA antibodies] bind to the target NMDA receptor located on a neuronal cell in the central nervous system and associated with a neurological disorder, and directly [modifies] modify the function of the target NMDA receptor, or indirectly [modifies] modify the function of a process involving the NMDA receptor[, such that the direct, or indirect modification protects against a neurological disorder].

98. (Amended) [The method of claim 95,] A method for modifying the function of a N-methyl-D-aspartate (NMDA) target receptor associated with a neurological disorder in the central nervous system of a subject comprising:

inducing the presence of a therapeutically effective amount of an NMDA antigen in the circulatory system of the subject, wherein the antigen is induced by a vaccine [is] selected from the group consisting of a viral vector vaccine, a DNA vaccine, a peptide vaccine and a crude antigen vaccine[.], such that the antigen elicits the production of NMDA antibodies in the circulatory system of the subject that, upon compromise of the blood-brain barrier, will pass into the central nervous system of the subject and bind to the target NMDA receptor located on a neuronal cell in the central nervous system and associated with a neurological disorder, and directly modify the function of the target NMDA receptor, or indirectly modify the function of a process involving the NMDA receptor.

102. (Amended) A method for modifying the function of a N-methyl-D-aspartate (NMDA) target receptor associated with cognition in the central nervous system of a subject comprising:

[administering a vaccine comprising] inducing the presence of a therapeutically effective amount of an NMDA antigen in the circulatory system of the subject, wherein the antigen elicits the production of NMDA antibodies that, upon compromise of the blood-brain barrier, will pass into the central nervous system of the subject and [in the circulatory system of the subject, or a composition comprising a therapeutically effective amount of an isolated NMDA antibody, or an antibody portion, wherein the NMDA antibodies] bind to the target NMDA receptor associated with cognition, and [modifies] modify the function of the target NMDA receptor such that the modification of the NMDA receptor improves cognition in the subject.

105. (Amended) [The method of claim 102,] A method for modifying the function of a N-methyl-D-aspartate (NMDA) target receptor associated with cognition in the central nervous system of a subject comprising:

inducing the presence of a therapeutically effective amount of an NMDA antigen in the circulatory system of the subject, wherein the antigen is induced by a vaccine [is] selected from the group consisting of a viral vector vaccine, a DNA vaccine, a peptide vaccine and a crude antigen vaccine[.], such that the antigen elicits the production of NMDA antibodies that, upon compromise of the blood-brain barrier, will pass into the central nervous system of the subject and bind to the target NMDA receptor associated with cognition, and modify the function of the target NMDA receptor such that the modification of the NMDA receptor improves cognition in the subject.

109. (New) A method for modifying the function of a target receptor associated with a neurological disorder in a subject comprising:

administering a vaccine comprising a therapeutically effective amount of an N-methyl-D-aspartate receptor subunit 1 (NMDAR1) antigen into the circulatory system of the subject, wherein the antigen elicits the production of antibodies that, upon compromise of the blood-brain barrier, will pass into the central nervous system of the subject and bind to a target receptor located on a neuronal cell in the central nervous system of the subject and associated with a neurological disorder, and modify the function of the target receptor.

REMARKS

Claims 1-3, 5-12, 22-32, 36-44, 54, 59-61, 68, 70-72, 74-76 and 86-109 are pending in the present application. Claims 4, 13-21, 33-35, 47-53, 55-58, 62-67, 69, and 77-85, drawn to a non-elected invention, have been withdrawn from consideration by the Examiner, in light of Applicant's election with traverse to pursue the invention of group (I), as recited by claims 1-3, 5-12, 22, 25-32, 36, 38-44, 54, 56-68, 70 and 72-74. In Paper No. 15 at page 16, lines 3-4, Applicant canceled claims 4, 13-21, 33-35, 47-53, 55-58, 62-67, 69, and 77-85 with traverse. Applicant reserves the right to file a divisional application for the non-elected claims or to reinstate certain claims upon the allowance of one or more generic claims.

Claims 1-3, 5-12, 22-32, 36-44, 54, 59-61, 68, and 86-108 of the application have been rejected by the Examiner. Applicant respectfully notes that the Examiner has withdrawn some of the substantive rejections of the pending claims. In particular, the Examiner has withdrawn the rejections under 35 U.S.C. § 112, second paragraph with regard to claims 9, 29, 41, and 59.

Claims 70-72 and 74-76 have been cancelled. Claims 1, 6, 9, 22, 24, 25, 29, 36, 38, 41, 54, 59, 68, 86, 91, 95, 98, 102 and 105 have been amended and new claim 109 has been added. Support for the amendments and new claim language can be found throughout the specification, or the claims as originally filed. For example, support for the phrase "inducing the presence of a therapeutically effective amount of an antigen in the circulatory system of the subject" can be found at page 2, lines 14-18; at page 15, lines 29-31; and at page 30, line 27 through page 35, line 3. Support for the phrase "upon compromise of the blood-brain barrier, will pass into the central nervous system of the subject" can be found, for example, at page 2, lines 18-24; at page 35, lines 11-14; and at page 37, lines 16-20. Support for the phrase "the presence of a therapeutically effective amount of the antigen in the circulatory system of the subject is induced by a vaccine" can be found, for example, at page 30, line 27 through page 35, line 3; and at page 37, lines 26-29. No new matter has been added.

Amendment of the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and was done solely to more particularly point out and distinctly claim the

invention to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

In the Office Action of October 1, 2002, the Examiner asserts that Applicant's response filed July 2, 2002 was not fully responsive because the amended claims were no longer directed to the restricted subject matter presently undergoing examination. Applicant respectfully disagrees. This application was subject to a Restriction requirement pursuant to Paper 6 to which Applicant responded by electing the Group I invention (claims directed to treatment of a neurological disorder by administering a vaccine). The amendments to the claims do not depart from this election but rather present several genus level claims that encompasses both the elected subject matter and other aspects of the invention.

See, for example, amended claim 1 which now recites a method comprising "*inducing the presence of a therapeutically effective amount of an antigen in the circulatory system of the subject...*" and amended claim 9 which specifies that "*the presence of the therapeutically effective amount of an antigen in the circulatory system of the subject is induced by a vaccine...*"

Applicant has not redirected his claims to a new patentably distinct invention, as suggested in the Office Action. To the contrary, Applicant has presented genus level linking claims, which he legally entitled to do at any stage in prosecution. *Cf.* Section 809 of the Manual of Patent Examining Procedure:

The linking claims must be examined with the invention elected, and should any linking claim be allowed, the restriction requirement must be withdrawn.

To ensure that this supplemental amendment is deemed responsive, Applicant has also rewritten claims 9, 29, 41, 59, 91, 98, and 105 in independent form and added new claim 109, all of which are specifically drawn to a treatment of a neurological disorder by administering a vaccine. If the Examiner is still of the opinion that the amendments to principal claims 1, 22, 36, 54, 86, 95, and 102 are non-responsive, the appropriate action is believed to be to enter the amendment but treat the pending claims other than those that specifically recite treatment by

vaccine administration (i.e. claims 9-12, 29-32, 41-44, 59-61, 91-94, 98-101 and 109) as withdrawn from prosecution. Should the Examiner take such a position, Applicant requests an explanation of the reasons why the amendments to the principal claims do not constitute generic claims linking species.

The remainder of these remarks address the issues raised in the Office Action of February 27, 2002, first with regard to the generic claims and then with respect to the species claims.

Objections to the Specification

The Examiner has objected to the title as “not descriptive.” To expedite prosecution of the above-referenced application, Applicant has amended the title to “Method for Modifying Target Receptor Function Associated with Neurological Disorders.” The new title is clearly indicative of the invention to which the claims are directed. Accordingly, Applicant respectfully requests that the Examiner withdraw this objection.

Claim Objections

The Examiner has objected to claims 1-3, 5-12, 22-32, 36-44, 54, 59-61, 68, 70-72, 74-76, and 86-108, as reciting a non-elected group, and in particular, for reciting the step of “administering a composition comprising an isolated antibody.” Applicant notes that claims 70-72 and 74-76 have been canceled, thereby rendering any objections to these claims moot. Applicant also notes that the pending claims, as amended, do not recite a “composition comprising an isolated antibody,” thereby obviating this objection. Applicant, therefore, respectfully requests that Examiner withdraw this objection.

The Examiner has also objected to claims 3, 6-8, 24-28, 38-40, 68, 72, 75-76 and 88 as reciting “non-elected species of disorders and type of target protein/antigen.” Each of the claims to which this objection applies is a so-called “Markush-type” claim. In this regard, the Examiner’s attention is directed to MPEP Section 803.02:

Following election, the Markush-type claim will be examined fully with respect to the elected species and further to the extent necessary to determine patentability.

Accordingly, Applicant wishes to defer any amendments to these claims pending a final decision regarding the allowability of species and/or generic subject matter.

Rejection of Claims 1-3, 5-12, 22-32, 36-44, 54, 59-61, 68, 70-72, 74-76 and 86-108 Under 35 U.S.C. § 112, First Paragraph

Claims 1-3, 5-12, 22-32, 36-46, 54, 59-61, and 68 remain rejected under 35 U.S.C. §112, first paragraph as “containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with it is most nearly connected, to make and/or use the invention.” In particular, the Examiner asserts that:

Specifically, Applicant has not provided evidence to demonstrate the modification of the function of any target receptor associated with a neurological disorder, cognition, or a neuroendocrine disorder in a subject by administration of a peptide vaccine comprising an antigen (NMDAR1). The specification teaches subcloning of the full length mouse NMDAR1 cDNA into adeno-associated virus (AAV) plasmid to yield a recombinant virus, AAVNMDAR1 (pg 54, lines 14-19). The specification also teaches the peroral administration of this vector to groups of rats (pg 54, lines 19-22; pg 59-75). The specification discloses NMDAR1 protein expression and the presence of circulating antibodies in rats administered the genetic vaccine (pg 55-57). However, the specification provides no guidance or working examples for the administration of a NMDAR1 antigen peptide vaccine and modification of the function of any target receptor in a subject. The examples in the specification disclose the deliver of the full length mouse NMDAR1 *gene* into rats while the claims of the instant application recite the delivery of an *antigen* into a subject. The working examples in the specification directed to administration of the genetic vaccine (as reviewed in Applicant’s arguments above) do not provide guidance regarding the administration of a protein vaccine to subjects. Additionally, there is no guidance or working examples in the specification to indicate that if administered, the NMDA antigen produces anti-NMDA antibodies and that the antibodies bind to a target receptor on a neuronal cell to directly modify the receptor or indirectly modify the function of a process involving the receptor *in vivo*. Example 6 in the Specification only describes (i) an *in vitro* assay utilizing primary mesencephalic rat neuronal cultures and purified IgG from AAVNMDAR1 vaccinated rats and (ii) an immunohistochemistry assay of Krox-24 levels in the cortex of AAVNMDAR1 treated rats. (Office Action, pages 6-7).

Although Applicant respectfully disagrees with the basis of this rejection, in order to expedite prosecution of the present application, Applicant has amended the claims, and in particular, Applicant has amended independent claims 1, 36, 54, 86, 95 and 102 to include the step of “inducing the presence of a therapeutically effective amount of an antigen in the circulatory system of the subject” to elicit the production of a therapeutically effective amount of antibodies in the circulatory system of a subject.

The salient features of the claimed methods, as amended, involve using antibodies that are produced in response to the presence of a central nervous system antigen in the systemic circulatory system of the subject. These antibodies circulate in the circulatory system until the blood-brain barrier has been compromised. Upon compromise of the blood-brain barrier, these circulating antibodies can cross the blood-brain barrier, can pass into the central nervous system of the subject, and can bind to, and modify the function of, a target receptor associated with a neurological disorder (*e.g.*, a neurological disease, a neuroendocrine disorder, or cognition). These antibodies can either directly modify the function of the target receptor on the neuronal cell, for example, by inhibiting receptor activity, or alternatively, they can indirectly affect the function of the target receptor, for example, by altering a protein or a downstream process that is associated with the target receptor.

Thus, it is clear that the amended claims are no longer drawn to the administration of a vaccine comprising a therapeutically effective amount of an antigen, but rather to the *presence* of a therapeutically effective amount of an antigen *in the circulatory system of a subject*, such that the antigen elicits the production of antibodies that can pass into the central nervous system of the subject upon compromise of the blood-brain barrier. The means by which the antigen is introduced into the circulatory system of the subject is irrelevant to the efficacy of the claimed methods in treating a neurological disorder, in treating a neuroendocrine disorder, and in improving cognition. Accordingly, the Examiner’s rejection has been rendered moot by these claim amendments, and Applicant respectfully requests that the Examiner withdraw this rejection.

The claims, as amended, recite methods that are sufficiently enabled by the specification of the present invention to provide one of ordinary skill in the art with adequate guidance to modify the function of a target receptor associated with a neurological disorder, a neuroendocrine disorder, or cognition, by raising antibodies against a central nervous system antigen present in the circulatory system of a subject. In particular, the specification of the present application describes in detail how the presence of a central nervous system antigen can be induced in the circulatory system of a subject. As disclosed at pages 30-35, “[g]enerally, the antigen is delivered to the systemic circulatory system using methods known in the art.” These methods include the direct administration of the antigen into the systemic circulatory system of a subject, such as for example, by peroral administration of the antigen or intramuscular injection of the antigen. The disclosed methods also include, however, the indirect administration of the antigen into the systemic circulatory system, such as for example, by the delivery of DNA encoding the central nervous system antigen, which can then be used to express the antigen, thereby inducing the presence of the antigen in the circulatory system of the subject. According the specification at pages 30-32 and 34-35, this DNA can be delivered to a subject in a variety of ways, such as for example, by vaccination with a viral vector construct containing an exogenous nucleic acid molecule encoding the desired antigen, by liposome delivery or by vaccination using a gene-gun-based delivery, in which the DNA can be delivered as naked DNA without an expression vector, or alternatively, the DNA can be inserted into an expression vector.

Furthermore, the specification clearly demonstrates that these circulating antibodies can migrate across the blood-brain barrier, once the blood-brain barrier has been compromised, and can bind to, and modify the function of a target receptor located on a neuronal cell in the central nervous system. To illustrate this aspect of the claimed methods, the specification provides examples using the NMDA receptor, which is located on a neuronal cell in the central nervous system of a subject, as the target receptor. (*See e.g.*, Examples 2(iii), 3-5 and 7). These examples demonstrate that the NMDAR1 protein, when delivered to the circulatory system of a rat model of a neurological disorder, can be used as an antigen to generate antibodies against the NMDA receptor. These examples also demonstrate that the antibodies against the NMDA receptor can cross the blood-brain barrier, can bind to the NMDA receptor, and can modify the

function of the NMDA receptor. Evidence that the function of the NMDA receptor has been modified includes, for example, evidence of the neuroprotective efficacy of the method of the claimed invention against neurological disorders including epilepsy (*See Example 3*) and stroke (*See Example 4*). The specification also contains evidence of the efficacy of the claimed method in improving cognition in rat models (*See Example 7*).

Thus, these teachings provide adequate guidance to enable one of ordinary skill in the art to modify the function of a target receptor associated with a neurological disorder, a neuroendocrine disorder, or cognition, by raising antibodies against a central nervous system antigen present in the circulatory system of a subject. In fact, at pages 6-7 of the Office Action, the Examiner admits that the specification “discloses NMDAR1 protein expression and the presence of circulating antibodies in rats.” Because the specification adequately teaches a method for modifying the function of a target receptor using circulating antibodies that can cross the blood-brain barrier upon compromise, the disclosure is sufficient to enable one of ordinary skill in the art to make and use the claimed methods to treat a neurological disorder, a neuroendocrine disorder, or to improve cognition in a subject. Accordingly, Applicant respectfully requests that the Examiner allow the claims as amended.

At page 7 of the Office Action, the Examiner has also asserted:

The specification also does not teach which specific neuronal cell(s) the target NMDA receptor is present on. Numerous types of neuronal cells are present in the central nervous system of a subject, such as dopaminergic neurons, serotonergic neurons, oligodendrocytes, Schwann cells, and astrocytes. Therefore, regarding the instant application, undue experimentation would be required of the skilled artisan to modify the function of a target receptor on any neuronal cell associated with a neurological disorder, cognition, or neuroendocrine disorder in a subject by administration of an NMDA antigen.

It is believed that this rejection applies to claims 1-3, 5-12, 22-32, 54, 59-61, 68, 70-72, 74-76, and 86-101, which recite the term “neuronal cell.” These claims have been amended, and in particular, independent claims 1, 22, 54, 86 and 95 have been amended to recited antibodies that “bind to a target receptor located on a neuronal cell in the central nervous system of the subject and associated with a neurological disorder.” These amendments, which further refine

the target receptor and its location in the central nervous system, are sufficient to overcome the Examiner's concerns that the term "neuronal cell" is too broad to be enabled by the present specification. These claims do *not* cover any or all neuronal cells. On the contrary, these claims are directed to neuronal cells that have the desired target receptor and that are associated with a neurological disorder, a neuroendocrine disorder, or cognition.

Applicant, therefore, respectfully disagrees with the Examiner's characterization that undue experimentation would be required of the skilled artisan to modify the function of a target receptor on any neuronal cell, because the present invention is not directed to the modification of all neuronal cells, but rather, only to those that have the selected target receptor and are associated with a neurological disorder. Accordingly, Applicant respectfully requests that the Examiner withdraw this rejection.

Additionally, the Examiner has also asserted that:

[T]he specification does not teach "protecting against" a neurological disorder or a neuroendocrine disorder by modifying the function of a receptor in a subject. The phrase "protecting against" is interpreted as meaning that an activity will not occur, i.e. a neurological or neuroendocrine disorder will not manifest/occur. Undue experimentation would be required of the skilled artisan to determine the quantity of antigen to be administered, the best route of administration, the duration of treatment, and any possible side-effects in order to generate antibodies which bind to and modify the function of the target receptor, such that modifying the function of the target receptor protects against a neurological disorder. (Office Action, page 8).

It is believed that this rejection applies to claims 1-3, 5-12, 22-32, 54, 59-61, 68, 70-72, 74-76, 86-101, which, prior to Applicant's proposed amendments, contained the offending term "protecting against." Applicant notes that the offending term has been removed, and therefore, this rejection has been rendered moot. Accordingly, Applicant respectfully requests that the Examiner withdraw this rejection.

On page 8 of the Office Action, the Examiner has also concluded that:

[A]lthough the state of the art at the time the application was filed demonstrates the preparation of NMDAR1 peptide or fusion proteins with NMDAR1 to generate antibodies, relevant literature indicates that numerous problems exist in regards to administering a subunit (antigen) vaccine to humans and animals. Several characteristics of an ideal vaccine, regardless of the species, must include: 1) efficacy greater than 90%, 2) effective after a single dose, 3) long lived immunity, 4) effective when given orally, and 5) high safety (Babiuk, LA. *Vaccine 17*: 1587-1595, 1999). Often, when some proteins are included in a vaccine, they may be immunosuppressive, but in other cases, the immune responses to proteins may enhance the disease (Babiuk, pg 1588, col 2). Although antigen vaccines have the advantage of increased safety, their major disadvantages are their low level of immunogenicity and rapid degradation *in vivo*. The rapid degradation *in vivo* may explain the low immunogenicity, even if linked to a carrier or strong adjuvant (pg 1588, col 2; pg 1590, col 2). (Office Action, page 8).

It is believed that this rejection applies to claims 1-3, 5-12, 22-32, 36-44, 54, 59-61, 68, 70-72, 74-76, and 86-108. However, this rejection has been rendered moot by the claim amendments, as described above. All arguments recited above are reiterated herein in their entirety. In particular, Applicant notes that independent claims 1, 22, 36, 54, 86, 95 and 102 have been amended to include the step of "inducing the presence of a therapeutically effective amount of an antigen in the circulatory system of the subject" to elicit the production of a therapeutically effective amount of antibodies in the circulatory system of a subject. Thus, these amended claims are no longer drawn to the administration of a vaccine comprising a therapeutically effective amount of an antigen, but rather to the *presence* of a therapeutically effective amount of an antigen *in the circulatory system of a subject*, such that the antigen elicits the production of antibodies that pass into the central nervous system of the subject upon compromise of the blood-brain barrier. As the amended claims are no longer directed to the specific means by which a central nervous system antigen is introduced into the circulatory system of a subject, the Examiner's rejection has been rendered moot. Accordingly, Applicant respectfully requests that the Examiner withdraw this rejection.

On pages 9-12 of the Office Action, the Examiner has asserted:

Specifically, the specification does not teach a composition comprising any antigen, which is capable of eliciting the production of antibodies in the

circulatory system of the subject. The assertion that other NMDA antigens can be readily substituted for NMDAR1 cannot be accepted in the absence of supporting evidence, because the relevant literature reports examples of polypeptide families wherein the individual members have distinct, and sometimes even opposite, biological activities. ...

Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence database. ...

Therefore, based on the discussions above concerning the specific examples of structurally similar proteins that have different functions, along with the art's recognition that one cannot rely upon structural similarity alone to determine functionality, the specification fails to teach the skilled artisan how to use other NMDA receptor subunit families without resorting to undue experimentation to determine what the specific biological activities of each family member are.

Proper analysis of the Wands factors was provided in the previous Office Action. Due to the large quantity of experimentation necessary to modify the function of a target receptor associated with a neurological disorder, cognition, or neuroendocrine disorder by administration of an antigen vaccine and to determine an activity of other NMDA receptor subunit family members, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, and the unpredictability of the response and longevity of the antigen vaccine *in vivo* (see discussion and recited reference), the state of the prior art establishing that biological activity cannot be predicted based on structural similarity, and the breadth of the claims which embrace a broad class of structural NMDA variants, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

Applicant assumes that this rejection under 35 U.S.C. § 112, first paragraph, applies to claims 1-3, 5-12, 22-32, 36-44, 54, 59-61, 68, 70-72, 74-76 and 86-108. Applicant respectfully traverses this rejection, as the Examiner is attempting to use this rejection to limit the scope of Applicant's claims to cover only the embodiment of the invention that is disclosed in the working examples. The specification of the present invention provides adequate teaching and guidance to enable one of ordinary skill in the art to make and use the claimed methods of the present invention to modify the function of a variety of target receptors associated with neurological disorders. As described above, the amended claims clearly recite methods that are sufficiently enabled by the specification of the present invention to provide one of ordinary skill

in the art with adequate guidance to modify the function of a target receptor associated with a neurological disorder, a neuroendocrine disorder, or cognition, by raising antibodies against a central nervous system antigen present in the circulatory system of a subject. All arguments recited above regarding the enablement of the claims, as amended, are reiterated herein. Accordingly, Applicant is entitled to a claim coverage for all subject matter that one of ordinary skill in the art would gather from the teachings and guidance of Applicant's specification.

The working examples provided by the specification of the present invention are *merely illustrative* of the underlying inventive concept of Applicant's invention – they do *not* represent the sum total of Applicant's underlying inventive concept. As discussed above, the underlying inventive concept of the claimed methods involves the production of antibodies that have been raised against a central nervous system antigen circulating in the systemic circulatory system of a subject. These antibodies circulate in the circulatory system until the blood-brain barrier has been compromised. Upon compromise of the blood-brain barrier, these circulating antibodies can cross the blood-brain barrier, can pass into the central nervous system of the subject, and can bind to, and modify the function of, a target receptor associated with a neurological disorder, a neuroendocrine disorder, or cognition. These antibodies can either directly modify the function of the target receptor on the neuronal cell, for example, by inhibiting receptor activity, or alternatively, they can indirectly affect the function of the target receptor, for example, by altering a protein or a downstream process that is associated with the target receptor. Thus, the NDMAR1 working examples provided in Applicant's specification simply represent *one* embodiment of this underlying concept.

Accordingly, the scope of Applicant's claimed methods should not be limited to only the NMDAR1 antigen, because Applicant has provided adequate disclosure for other suitable antigens that can be readily substituted into the methods disclosed by the present specification to generate circulating antibodies that can cross a compromised blood-brain barrier and bind to a target receptor. For example, at page 16, line 14 through page 17, line 13, Applicant has disclosed other NMDA receptor subunit families, as well as a number of references that would direct one having ordinary skill in the art to further information regarding these NMDA receptor

subunit families. Furthermore, Applicant should not be limited to only the NMDA receptor subunit families, because the specification also discloses other suitable antigens for use in the claimed methods of the present invention. These additional, suitable antigens include, but are not limited to, transporters, ions channels, and neurotransmitters. (See pages 16-22 of the present application).

Likewise, the scope of the claimed methods should not be limited to cover only the use of NMDA receptors as the target receptors, because Applicant has provided adequate guidance for other suitable target receptors that can be readily substituted and used in the claimed methods of the present invention. For example, at page 15, line 23 through page 22, line 26 of the present application, Applicant has included a wide variety of suitable target receptors, which include NMDA receptors, neuronal glutamate (GluR) receptors, g-aminobutyric acid receptors (GABAR's), nicotinic acetylcholine receptors, serotonin receptors and dopamine receptors.

Additionally, Applicant has disclosed and provided guidance for a number of *in vivo* animal models of neurological disorders, which can be used to test the efficacy of any alternative NMDA receptor subunit antigens, or alternative suitable target receptors that are used in the claimed methods of the present invention. Likewise, Applicant has also disclosed a number of behavioral tests to determine the cognitive effects, if any, that may accompany the use of other suitable antigens or suitable target receptors in the claimed methods. In light of these disclosures, Applicant's specification clearly provides adequate guidance for testing and using additional suitable antigens and additional suitable target receptors for use in the disclosed methods of the present invention to generate antibodies that can cross a compromised blood-brain barrier and modify the function of the selected target receptor.

Applicant's claims are entitled to have a scope that cover all subject matter that is adequately enabled by the disclosure in the present specification. Here, the relative level of skill in the art is fairly sophisticated, and consequently, a person having ordinary skill in this art would be familiar with a large number of target receptors associated with neurological disorders. Accordingly, it would not constitute undue experimentation for a skilled artisan, upon reading Applicant's specification, to identify other target receptors for use in the claimed methods of the

present invention. Once the skilled artisan is aware that neurological diseases and neuroendocrine disorders can be treated, or cognition can be improved, by the production of circulating antibodies that can cross a compromised blood-brain barrier, it is merely routine experimentation to run the identified target receptors through the claimed methods in order to test their efficacy in treating neurological disorders.

Based on the teachings and guidance provided by the present specification, one of ordinary skill in the art could, without undue experimentation, readily test not only other suitable antigens, but also other suitable target receptors for use in the claimed methods. Accordingly, Applicant respectfully requests that the Examiner withdraw this rejection.

For all of these foregoing reasons, Applicant respectfully requests that the Examiner withdraw all rejections under 35 U.S.C. § 112, first paragraph.

Rejection of Claims 70-72 and 74-76 Under 35 U.S.C. §112 Second Paragraph

Claims 70-72 and 74-76 have been rejected under 35 U.S.C. § 112, second paragraph as being “indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.”

Applicant notes that claims 70-72 and 74-76 have been canceled, thereby obviating any rejection of these claims. Accordingly, Applicant respectfully requests that the Examiner withdraw this rejection.

Rejection of Claims 70-76 Under 35 U.S.C. §102

Claims 70-76 have been rejected under 35 U.S.C. § 102, as having been anticipated by Luo *et al.* (Molec. Pharmacol. 51: 79-86 (1997)). In particular, the Examiner has asserts that:

Luo *et al.* teach a composition comprising an NMDA antigen capable of eliciting the production of NMDA antibodies in the circulatory system of a subject. Luo *et al.* disclose the expression of a fusion protein using a vector generated by ligating the cDNA encoding amino acids 1-561 from the NMDAR1A sequence into the BamHI site of the plasmid pET 14b. Samples are aliquoted, lyophilized, and stored until use (pg 80, ¶ 4). Luo *et al.* also teach that

the purified protein is resuspended in either Freund's complete adjuvant or Freund's incomplete adjuvant and injected into mice (pg 80, col 1-2). Antibodies are generated and purified over an affinity column. Please note that a compound and all of its properties are inseparable; they are one and the same thing (see *In re Papesch*, CCPA 137 USPQ 43). Simply stating a new property of the NMDAR1 antigen or antibody of Luo *et al.* does not render the composition comprising an NMDA antigen that elicits the production of NMDA antibodies (and wherein the NMDA antibodies bind an NMDA receptor and modify the function of the NMDA receptor such that the modification of the NMDA receptor protects against a neurological disorder) of the instant application free of the art. (Office Action, pages 12-13).

Applicant notes that claims 70-72 and 74-76 have been canceled, thereby rendering any rejection of these claims moot. Accordingly, Applicant respectfully requests that the Examiner withdraw this rejection.

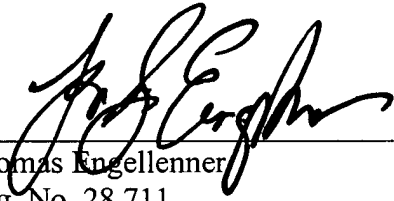
CONCLUSION

In summary, the above-identified patent application has been amended and reconsideration is respectfully requested for all the reasons set forth above. The Examiner is urged to telephone the undersigned Attorney for Applicant in the event that such communication is deemed to expedite prosecution of this matter.

Respectfully submitted,

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Date: 3 Feb 2003



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